

# **The correlation of the ovarian and uterine functions / by E.S. Carmichael.**

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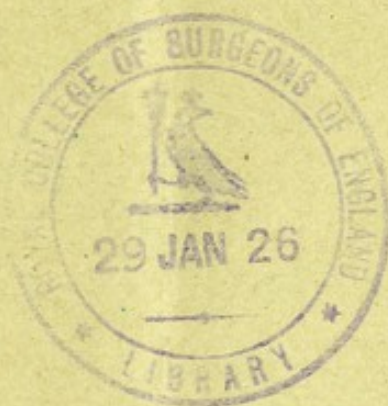


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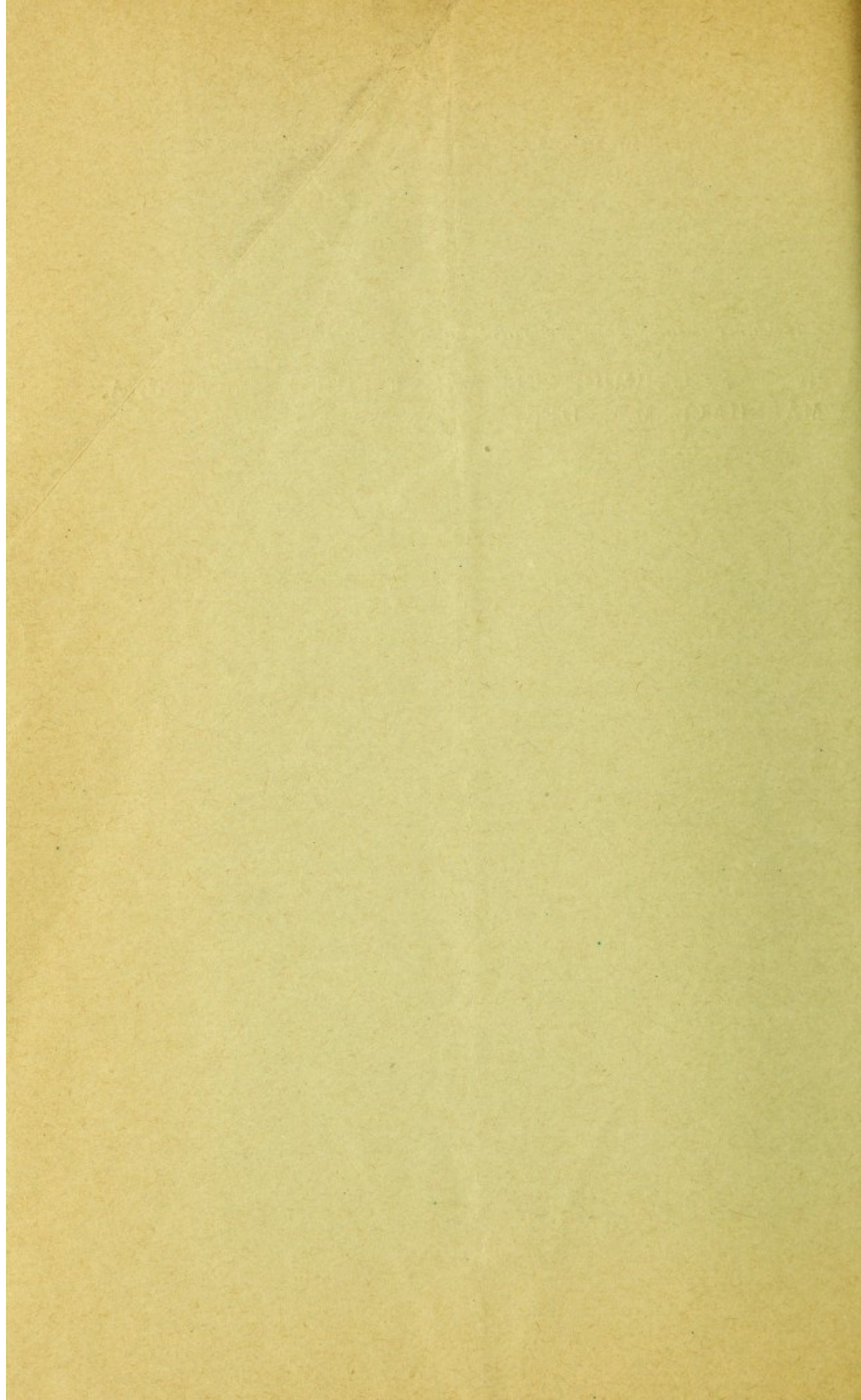
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*The Correlation of the Ovarian and Uterine Functions.*

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*The Correlation of the Ovarian and Uterine Functions.*

By E. S. CARMICHAEL, M.B., F.R.C.S.E., and F. H. A. MARSHALL, M.A., D.Sc.

(Communicated by Professor E. A. Schäfer, F.R.S. Received April 10,—  
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(From the Physiological Laboratory, University of Edinburgh.)

A considerable body of evidence has been adduced in support of the hypothesis that the uterus is dependent upon ovarian influence for the maintenance of its structure and the discharge of its functions, and that the removal of this influence at any time during reproductive life causes the uterus to atrophy, besides producing a profound effect upon the entire metabolism of the organism. Some writers, on the other hand (*e.g.*, Blair Bell), contend that it is the uterus which is of prime importance, and observations have recently been cited pointing to the conclusion that this organ exercises a control over the growth and activity of the ovaries. Others, again (*e.g.*, Bond), adopt the view that the ovaries and uterus are to a very large extent inter-dependent upon each other.

The clinical evidence brought forward by surgeons after removal of the uterus and ovaries in the human subject has supported to a great extent the experimental evidence of the existence of such an inter-relation. The modern tendency to conserve these organs as far as possible during surgical interference has been brought about largely by the belief in the dependence of the one organ upon the other. Important work bearing upon this subject has been published recently by Zweifel (1899), Mandl and Bürger (1904), Bond (1906), and many other surgeons.

It is the purpose of this paper to record a series of experiments dealing



with these questions, and to state the conclusions which we have reached regarding them.

*Influence of the Ovary upon the Uterus.*

A brief *résumé* of the experimental evidence adduced upon the existence and nature of the ovarian influence has been recently given in a paper by Marshall and Jolly (1907), who cite observations showing that the uterus undergoes undoubted degenerative changes after the removal of the ovaries. Further evidence, which is in accord with this conclusion, has been independently reached by Carmichael (1907). For accounts of the literature reference may be made to these papers.

Since, however, certain of the conclusions arrived at are still matters of controversy,\* it has been thought worth while to place on record the results of further experiments upon rabbits, dealing, firstly, with the effects of ovariectomy in full-grown adults at different periods after the operation, and secondly, with the effects of the same operation in young animals.

It has been suggested that the changes occurring in the uterus may be due to an interference with the blood supply to that organ, in the removal of the ovary. The uterus in the rabbit, as in the human subject, has an independent vessel of supply derived from one of the pelvic vessels, and it is inconceivable that any operation undertaken with care for the removal of the ovaries, situated as they are high up in the abdominal cavity, could interfere with this vessel. Care was also taken in our experiments to avoid injuring the anastomotic branch of the ovarian artery, which passes along the Fallopian tube to join the uterine.

For this purpose in several of the experiments a lateral incision was made over the ovary on each side, so as to obtain better access and interfere with the mesovarium as little as possible by traction, a condition which is unavoidable in removal of the ovaries by a mesial incision. Thus all dangers of fallacy from vascular interference were avoided.

A mesial incision is often unsatisfactory for the removal of ovaries, in that the upper pole of the ovary may be left behind in dividing its superior attachment, considerable traction being required to expose the organs freely.

In the following experiments fully grown rabbits were used:—

*Experiment 1.*—The ovaries were removed by a mesial incision, and the animal killed after an interval of three and a-half months. Sections showed that the uterine stroma had undergone considerable fibrosis and was reduced in amount. The glands had almost entirely disappeared. The superficial epithelium was, however, fairly normal, but degenerated in places, some

\* See the latter part of the present paper, where recent theories upon the nature and importance of the uterine influence are discussed.



of the cells being vacuolated. The muscular wall did not show much degeneration, but was somewhat thinner than usual. Superficially the uterus, whose size was carefully noted at the time of the operation, was perceptibly smaller.

*Experiment 2.*—The ovaries were removed by a mesial incision, and the animal killed three and a-half months subsequently, as in the preceding experiment. The glands and epithelium did not show the same degree of degeneration as in the previous case. Some fibrosis was, however, clearly discernable throughout the stroma. The muscles appeared to be not well developed, but otherwise were fairly normal.

*Experiment 3.*—The ovaries were removed from a pregnant rabbit by two lateral incisions. Two days afterwards the rabbit aborted. After five and a-half months the rabbit was killed. The uterus appeared very pale and atrophic looking. Mammary tissue was almost non-existent. Adipose tissue was super-abundant. Sections through the uterus showed that the mucosa was very thin and also fibrotic, the nuclei of the stroma being few and far between, excepting in the immediate neighbourhood of the epithelium, just below which they were much more numerous. The glands were represented by mere traces. The epithelial cells were somewhat degenerated, not taking on the stain so well as normally. There were very few blood-vessels.

*Experiment 4.*—The ovaries of a rabbit were extirpated by means of two lateral incisions a week after parturition. The animal was kept alive for five and a-half months, during which time it received 22 injections of commercial ovarian extract, made to determine whether this would have the effect of arresting the uterine degeneration. The extract was injected intra-peritoneally, one injection on an average being made every week. It was found, however, that whereas sometimes the injection appeared to result on the following day in a congestion of the mucous membrane of the external generative organs, the atrophy of the uterus was in no way prevented. Sections showed a very thin fibrotic mucosa, and a thin muscular coat. As in the preceding case, the glands had almost disappeared, and many of the epithelial cells were vacuolated and obviously degenerate. In the cervix the changes were not so pronounced, the epithelial cells being nearly normal in appearance.

*Experiment 5.*—The ovaries were removed by two lateral incisions. The rabbit was killed six and a-half months subsequently. Very pronounced changes had taken place. The uterine stroma was extremely fibrotic, and contained no glands. The epithelium was much attenuated, the nuclei having failed to take up the stain to the usual extent. A few very small



capillaries, however, could be still seen in the stroma. The muscle fibres were much broken up. The cervix had not undergone the same amount of degeneration, but some of the epithelial cells appeared vacuolated.

In the following two experiments very young immature rabbits were used :—

*Experiment 1.*—The ovaries were removed on May 29. The rabbit weighed 660 grammes. On August 8 it weighed 1640 grammes. On March 20 the rabbit was killed after first being weighed. The weight was 3450 grammes, the animal being fully grown and in perfect health. The uterus was found to be absolutely infantile, being no bigger than a rat's. Sections showed that the muscular wall was almost totally undeveloped. The mucosa was somewhat thicker, but fibrous throughout. The lining epithelium was, however, present.

*Experiment 2.*—The ovaries were removed from a very small rabbit on June 5. The animal weighed 740 grammes. On August 8 it weighed 1450 grammes. On March 20 it was killed after being first weighed. The weight at that time was 2080 grammes. The rabbit was quite fully grown and very fat. The uterus, as in the preceding experiment, was very small, being not so large as an adult uterus after the removal of the ovaries some months previously, as shown by our first series of observations.

These experiments show that the removal of the ovaries at an early period of life, while arresting the development of the other generative organs, has no effect on the growth and general health. The weights, as given above, compare favourably with those of unoperated rabbits and with those of animals in which the uterus had been removed (see below).

#### *Influence of the Uterus upon the Ovaries.*

Although the bulk of evidence brought forward clinically seems to show that the uterine functions fall into abeyance after removal of the ovaries, a considerable number of cases have been reported in which menstruation has persisted after oöphorectomy. Pozzi (1905) has recently recorded several such cases, but the uterus in the majority contained a uterine fibroid or other pathological condition.

The explanation of such cases has always been a difficult one, but it has probably led to the ideas now held by some surgeons that the uterus is capable of performing its functions independently of the ovaries, and even that the functions of the ovaries themselves depend largely on the presence of the uterus and its secretions.

Zweifel and Abel, in a communication to the German Gynæcological Congress (1899) in tracing the after-histories of cases of hysterectomy, found



that when the body of the uterus was removed, entire atrophy of the ovaries always followed, so that menopausal symptoms set in similar to those occurring after oöphorectomy. In three cases, however, in which a portion of the uterine mucous membrane was conserved, menstruation persisted and menopausal symptoms were absent.

Doran (1905), after following up the after-history of 60 cases of sub-total hysterectomy, is inclined to support Abel and Zweifel, in that the uterus should be removed above the cervix, in order to prevent sudden artificial menopause, while he also cites two cases where menstruation persisted after removal of the body of the uterus and both ovaries, the cervix being left behind.

Mandl and Bürger (1904) in an exhaustive monograph on the effects of hysterectomy with and without the ovaries hold that in those cases in which the ovaries are left behind there is a gradual cessation of ovarian function due to atrophy or degeneration of the ovaries.

Holzbach (1906), however, states that, as a rule, the ovaries do not degenerate after hysterectomy, and that where such degeneration does occur it is probably due to the interference with the nervous connections consequent upon the operation of removal.

Blair Bell (1906) holds that the theory of the internal secretion of the ovary is inconclusive, and that the clinical facts go to show that menstruation is due to a uterine secretion, and the menopause due to its absence, while he supposes ovulation itself to depend on the circulation of this secretion, which he calls "uterin." He mentions that there have been many cases in the Royal Infirmary at Liverpool in which ordinary menstruation continued after the removal of the ovaries, and makes further statements pointing to the conclusion that the ovaries invariably atrophy after the removal of the uterus.

Bond (1906), on the other hand, believes that the ovarian secretion is influenced by a saline secretion from the endometrium, the two, however, acting antagonistically to one another, so that prevention of the uterine secretion by hysterectomy favours hypertrophy of the ovary. Bond's view, therefore, is diametrically opposite to that of Blair Bell.

Bond records two experiments on the results of hysterectomy. In one of these the entire uterus of a rabbit was removed and the animal killed after five months. Both ovaries were found to be normal. In the other experiment the left uterine cornu only was extirpated and the rabbit killed after five months. The ovaries in this case also were in no way atrophied. Bond expresses the belief that the prevention by previous hysterectomy of the secretion of the saline fluid by the endometrium of the anæstrous uterus favours the overgrowth of luteal tissue in the ovary.



Stress has also been laid upon the well-known fact that whereas the corpora lutea of the ovary continue to undergo development for a considerable period of time if pregnancy supervene after ovulation, this hypertrophy soon ceases in the absence of pregnancy. Bond records an experiment on a rabbit in which the ovary after being grafted to an abnormal position contained a somewhat aberrant "corpus luteum of pregnancy" in association with a gravid uterus. Such observations are regarded by him as affording evidence of an internal uterine secretion (differing from that elaborated by the anæstrous uterus), acting on the ovaries and so inducing a growth of luteal tissue. It must be remembered, however, that the occurrence of pregnancy exercises a profound effect over the whole maternal organism, and not merely upon the condition of the ovaries.

Certain other authors have adopted views which imply a dependence of the ovaries upon some function of the uterus. Thus, Loewenthal (1884) appears to have held that ovulation occurs as a result of a stimulus in some way set up by the uterine changes of the proœstrum. Moreover, Heape (1900) has expressed the belief that œstrus (which depends normally upon the presence of the ovaries) "is possible only after the active changes due to proœstrum have taken place in the uterus," but this statement clearly applies to normal animals.

Excepting for the two experiments of Bond, which have just been referred to, no experimental work appears to have been published upon the effects of hysterectomy on the ovaries. The following experiments, therefore, notwithstanding the fact that the results reached were negative, are not without importance.

*Experiment 1.*—On April 8 the uterus was removed entire from a very young rabbit which weighed 420 grammes. On August 8 the weight was 1640 grammes. The rabbit was killed on November 11 after being weighed. The weight was then 2060 grammes, the animal being apparently fully grown. The ovaries were well developed, having increased greatly in size since the operation. On histological examination they were found to be normal, containing numerous growing Graafian follicles, and showing no signs whatever of degeneration.

*Experiment 2.*—On April 8, the uterus of a very young rabbit was removed, excepting the cervix. Weight, 390 grammes. On August 8 the weight was 1640 grammes. On November 11 the rabbit was killed. Weight, 1940 grammes. The ovaries were normal in every way.

*Experiment 3.*—On May 2 the uterus was removed entire from a young rabbit. Weight, 650 grammes. On August 8 the weight was 1660 grammes. The rabbit was put with the buck at intervals and noticed to copulate. On



January 20 it was killed when quite full grown and in perfect condition. Weight, 3020 grammes. The ovaries were extremely well developed and contained numerous discharged follicles.

*Experiments 4 and 5.*—In each experiment the uterus was removed from a very young rabbit, excepting the cervix, and the rabbit killed after several months (in the one case after eight months and in the other after 10 months). Œstrus was noticed in both cases after the animals had reached maturity. The ovaries in both cases were normal, those of one animal containing large follicles, and those of the other (which had been with the buck) recently ruptured follicles.

*Experiment 6.*—The uterus was removed entire from a very young rabbit on May 17. Weight, 470 grammes. In August the animal was observed to be ill and on August 28 was killed. The ovaries had undergone development since the operation and were normal in histological appearance.

*Experiment 7.*—The uterus and Fallopian tubes were completely removed from a young rabbit on December 9. The rabbit was killed on April 3, when the ovaries were found to be normal and to contain many follicles.

In four experiments on rats the uterus was removed entire in the month of July. Two of the rats were killed in January, when the ovaries showed no indications of degeneration. The other two were killed in April, the ovaries being large in size and containing many protruding follicles.

On the other hand, marked uterine degeneration has been recorded in rats after the removal of the ovaries for shorter intervals of time (Marshall and Jolly, 1907).

Further, in the case of a ferret in which the uterus was removed, the histological appearance of the ovaries was normal after three months, when the animal unfortunately died. The interval which had elapsed, however, was probably too short to admit of the deduction of definite conclusions.

It may be concluded as a result of these experiments that the growth and development of the ovaries are in no way dependent upon the presence of the uterus. Such a conclusion is no doubt in opposition to some of the clinical evidence, but it is one which on phylogenetic grounds might be expected, since the uterus is an organ which came into existence comparatively recently in the course of vertebrate evolution, whereas the ovary is common to all Metazoa.

It has been shown, further, that Œstrus and coitus may occur after the complete removal of the uterus. Whether under such a condition the other generative organs undergo any of the changes which normally characterise the proœstrum was not determined, since such changes are in any case difficult to detect in rabbits.



It was likewise impossible to determine definitely whether there was any increase of ovarian activity consequent upon hysterectomy (such as one would infer if Bond's theory of an antagonistic uterine secretion were correct), but we failed to discover any clear indication of its existence.

*Summary of Conclusions.*

The results obtained by these experiments lead us to summarise our conclusions as follows:—

1. The removal of the ovaries in young animals (rodents) prevents the development of the uterus and Fallopian tubes. These remain in an infantile condition. The subsequent growth and general nutrition of the animals seem to be unaffected.

2. The removal of the ovaries in adult animals (rodents) leads to fibrous degeneration of the uterus and Fallopian tubes (most marked in the mucous membrane). The animals' subsequent health and nutrition remain good.

These observations, for the most part, support the evidence obtained clinically in the human subject after surgical operation.

3. The removal of the uterus in a young animal has no influence in preventing the further development of the ovaries. These are capable of ovulating and forming corpora lutea after adult life has been reached.

4. The removal of the uterus in an adult animal does not give rise to any degenerative change in the ovaries, if the vascular connections of the latter remain intact.

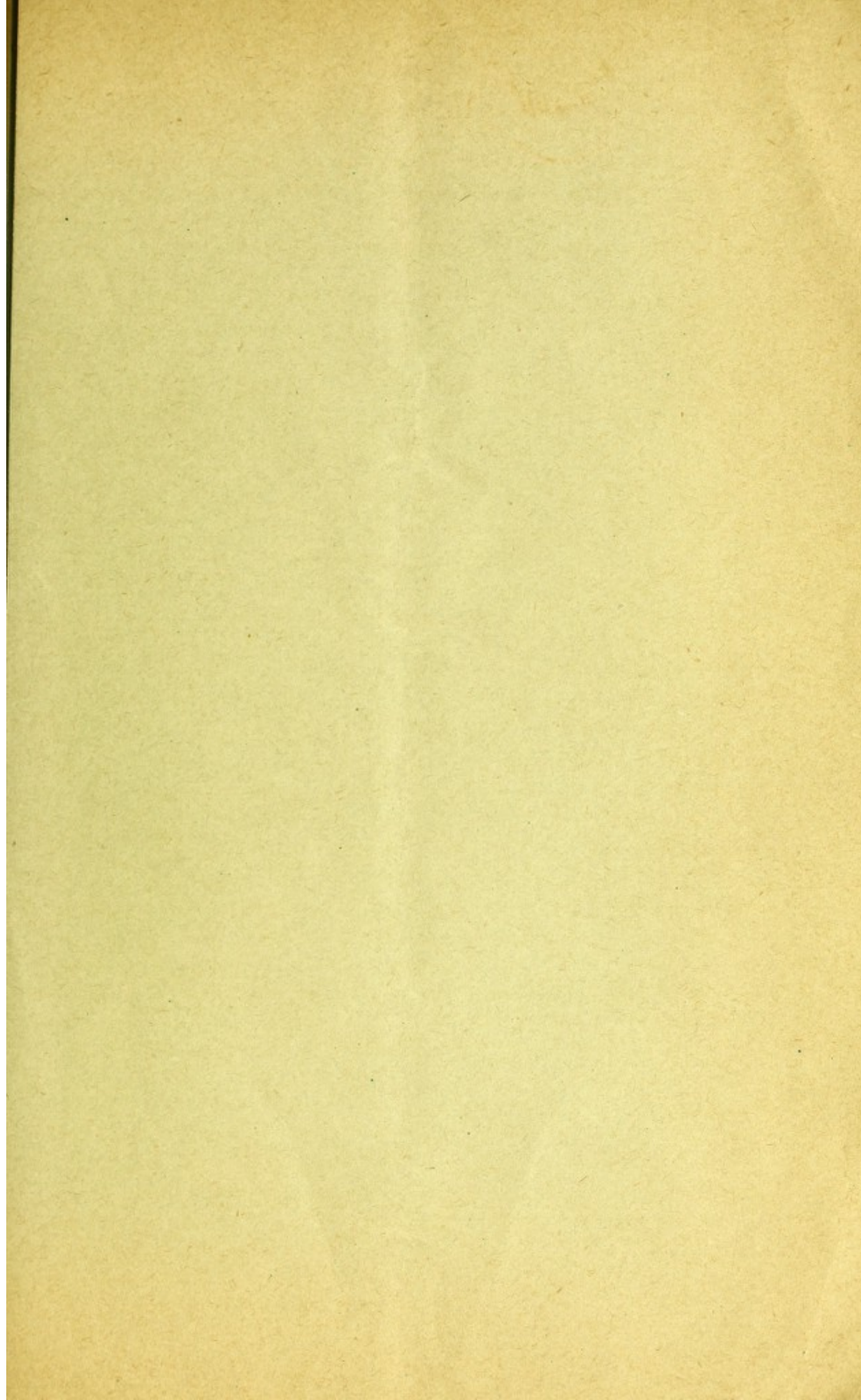
These latter observations do not support the contentions of those surgeons who advocate sub-total hysterectomy, believing that the functional activity of the ovary is in some way dependent on the presence of the uterus.

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